Long-term results of a randomized trial comparing three different devices for percutaneous closure of a patent foramen ovale

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Aims
Percutaneous patent foramen ovale (PFO) closure for secondary stroke prevention is discussed controversially. Long-term data comparing different closure devices are limited. The objective is the prospective comparison of procedural complications and long-term results after PFO closure in patients with cryptogenic stroke randomized to three different closure devices.

Methods and results
Between January 2001 and December 2004, 660 patients with cryptogenic stroke were randomized to three different closure devices (Amplatzer, CardioSEAL-STARflex, and Helex occluder, 220 patients per group). The primary endpoint was defined as recurrent cerebral ischaemia [stroke, transient ischaemic attacks (TIA), or Amaurosis fugax], death from neurological cause, or any other paradoxical embolism within 5 years after the index procedure.

Device implantation was technically successful in all interventions (n = 660; 100%). The procedure was complicated by pericardial tamponade requiring surgery in one patient (Amplatzer group) and device embolization in three patients (all Helex group). Thrombus formation on the device was detected in 12 cases (11 CardioSEALSTARflex, 1 Helex, 0 Amplatzer; P, 0.0001), of which 2 required surgery. Complete closure after single device implantation was more common with the Amplatzer and with the CardioSEAL-STARflex than with the Helex occluder: Amplatzer vs. Helex vs. CardioSEAL-STARflex: n = 217 (98.6%) vs. n = 202 (91.8%) vs. n = 213 (96.8%; P = 0.0012). Within 5 years of follow-up, the primary endpoint occurred in 25 patients (3.8%; 10 TIAs, 12 strokes and 3 cases of cerebral death). Compared with the CardioSEAL-STARflex (6%; 6 TIAs, 6 strokes, 1 cerebral death) and Helex groups (4%; 4 TIAs, 4 stroke, 1 cerebral death), significantly fewer events (P = 0.04) occurred in the Amplatzer group (1.4%; 2 strokes, 1 cerebral death).

Conclusion
Although procedural complications and long-term neurological event rates are low regardless of the device used, the recurrent neurological event rate was significantly lower after Amplatzer than after CardioSEAL-STARflex or Helex implantation. This has important implications regarding the interpretation of trials comparing PFO closure with medical management.

Keywords
Patent foramen ovale  •  Percutaneous closure

Introduction
In nearly 50% of all cases of cryptogenic stroke or transient ischaemic attacks (TIA), a patent foramen ovale (PFO) can be detected.1 A higher prevalence of PFO in patients with cryptogenic stroke1 and reported cases of thrombus-in-transit2,3 suggest that paradoxical embolism via a PFO can cause a stroke. Therefore, PFO closure for the prevention of neurological events has been the subject of intense investigation. Percutaneous closure is a safe treatment option with observational studies demonstrating low complication4 and high closure rates as well as a low incidence of recurrent neurological events after closure in patients with cryptogenic embolic...
This may be a limitation. Of note, complete closure at any time during follow-up was defined as no bubbles crossing during TEE examination. The baseline examination also included a 12-lead electrocardiogram and transthoracic echocardiography.

Randomization was ensured through selection of sealed envelopes at the outset of the study, enrolling 220 patients in each group. The device chosen for the particular intervention to be used was determined prior to the beginning of the intervention. Implantation was performed under local anaesthesia and TEE guidance. The Amplatzer PFO/ASD occluder, Helex septal occluder, and CardioSEAL-STARflex device were used. All devices had CE mark and were commercially available in Europe at the time of enrolment. Specifics of the devices, sizing, and procedural details were outlined previously. Within 24 h after the procedure or before discharge from the hospital, a transthoracic echocardiography was performed to verify the position of the occluder and to assess for pericardial effusion. All patients were prescribed 100 mg of aspirin and 75 mg of clopidogrel per day for the first 6 months after the procedure. Antiplatelet medication was verified 30 days, 3 and 6 months after the intervention. Endocarditis prophylaxis for the appropriate procedures was recommended for 6 months.

Follow-up investigations were not performed blinded. TEE studies were performed at 4 weeks and 6 months after the index procedure. Patients were evaluated for residual shunts and the incidence of potential adverse events. In some patients with residual shunt 6 months after the implant, further TEE examinations were performed at the discretion of the cardiologist. All patients were followed annually through office visits, questionnaires and phone calls, or by contacting the referring physicians. In our questionnaires, we asked for recurrent neurological events as well as for the necessity of hospitalization since the time of our last contact. We made use of all hospital and clinic reports, especially in those subjects who experienced recurrent cerebral ischaemia.

Follow-up visits at 30 days and 6 months included 12-lead electrocardiography. Thereafter, additional ECGs and Holter tests were performed only in the case of symptomatic status.

The primary endpoint of this long-term analysis was defined as a composite of TIA, stroke, or death from neurological causes or any other paradoxical embolism beginning at the time of randomization for 5 years of follow-up (including all periprocedural and in-hospital events).

### Methods

This is a randomized study comparing three different PFO closure devices for complete closure (the short-term results have previously been published) and the composite of stroke, TIA, cerebrovascular death, or any other paradoxical embolism from the time of randomisation to 5 years of follow-up (including periprocedural and in-hospital events). Long-term follow-up was planned at study initiation as additional events were anticipated. It was felt that the event rate between devices may not only differ in short term but also in intermediate and long-term follow-up. Importantly, to date, randomized long-term data examining devices in a randomized fashion are not available.

Six hundred and sixty patients were enrolled. Patients at least 18 years of age with a PFO and cryptogenic stroke and/or TIA and/or migraine and/or decompression sickness were included (indications and contraindications are shown in Table 1). The presence of a PFO was verified during transoesophageal echocardiography (TEE) and measurements made as previously described. Agitated saline was used as echocardiographic contrast medium to demonstrate a right-to-left shunt at rest or provoked by Valsalva manoeuvre. Bubbles were counted in the left atrium within three to five cardiac cycles after right heart opacification. The shunt was defined as mild in the case of 1–5 bubbles, as medium in the case of 6–20 bubbles, and as severe in the case of more than 20 bubbles crossing. Valsalva manoeuvres were repeated at least twice in every patient to confirm the size of the shunt. TEE was performed under local anaesthesia or, if necessary, with sedation using propofol.

### Table 1 Indications and contraindications for percutaneous PFO closure

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
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<tr>
<td>History of cryptogenic TIA</td>
<td>Active infective endocarditis, bacteraemia, sepsis</td>
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<td>or stroke</td>
<td>Intracardiac mass (thrombus, vegetation, tumour)</td>
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<tr>
<td>History of paradoxical</td>
<td>Anatomy in which the device size required would interfere with other intracardiac or intravascular structures, such as valves or pulmonary veins</td>
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<td>embolism</td>
<td>- Thrombus in the venous pathway to the right atrium</td>
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<tr>
<td>Decompression sickness</td>
<td>- Venous pathway, through which access to the defect is gained, is inadequate to accommodate the appropriate sheath size</td>
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<tr>
<td>Migraine</td>
<td>- Associated disease requiring heart surgery</td>
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<td>- Posterior, superior, inferior, (or anterior) rim &lt; 5 mm</td>
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<td></td>
<td>- Patients unable to take antiplatelet or anticoagulant therapy</td>
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<td></td>
<td>- History of a severe allergy to nickel</td>
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As TIA is often not considered an adequate endpoint in clinical stroke trials, we performed additional analysis comparing the stroke and (vascular) death rates between the three groups. In addition, we conducted an endpoint analysis combining neurological events and complications requiring surgery.

The sample size was computed using PS Power and Sample Size Calculations (Copyright 1997 by William D. Dupont and Walton D. Plummer) for studies that are analysed by $\chi^2$ tests. Calculations had been performed for interpretation of the previously published acute results only (technical success and PFO closure rates). Importantly, at the time of study initiation, no randomized trial data were available that allowed prediction of annual event rates or their reduction after PFO closure.

Statistical analysis was performed on an intention-to-treat principle. Continuous variables were expressed as mean plus standard deviation and minimum and maximum values, and in percentage as appropriate. The Kruskal–Wallis was used for comparison between the three groups. Categorical variables were compared using two-sided $\chi^2$ analysis with the Yates correction. Significance was assumed with a $P$-value of $<0.05$.

Hazards for the composite endpoint of stroke, TIA, and cerebral death were obtained using the Kaplan–Meier method and log-rank testing. All data were analysed using SPSS for Windows (Version 15.0, SPSS Inc.). The study was approved by the local ethical committee, and all patients had given written informed consent prior to the procedure.

### Results

Patent foramen ovale catheter closure was attempted in 660 patients (361 men, 299 women, mean age 49.3 ± 12.9 years, range: 18–84 years) between January 2001 and December 2004 (Figure 1). They fulfilled the criteria for PFO closure either by a history of cryptogenic ischaemic stroke ($n = 381$; 58%) and/or TIA ($n = 336$; 51%) and/or migraine ($n = 50$; 7.6%) and/or decompression illness ($n = 3$; 0.5%). One hundred and eighty subjects had a history of more than one ischaemic event (27%). Atrial septal aneurysms were present in 63 subjects (28%) in the Amplatzer group, in 95 (43%) in the Helex group, and in 82 (37%) in the CardioSEAL-STARflex group ($P = 0.0062$). Besides the differences found in regard to septal aneurysms before the procedure, there were no significant differences in baseline characteristics between the three groups. Coronary artery disease was defined as a history of myocardial infarction, coronary intervention, or coronary artery bypass grafting. The mean PFO diameters were 9.7 mm (2–21.2 mm; Amplatzer), 9.3 mm (2–25.7 mm; Helex), and 9.5 mm (2–19.5 mm; CardioSEAL). Device implantation for PFO closure was technically successful in all interventions. Most placement attempts were needed in the Helex group. In seven patients, the occluders were retrieved before release and exchanged for another Helex due to an unsatisfactory constitution. The longest procedural and fluoroscopic times were in the Helex group (33.5 ± 14.2 min; 6.6 ± 4.6 min), although these differed only slightly compared with the other groups (Amplatzer: 28.6 ± 13.2 min, 4.1 ± 3.4 min; CardioSEAL-STARflex: 31.4 ± 12.2 min, 4.9 ± 3.5 min). The mean hospital stay time was longest in the CardioSEAL-STARflex group (19.8 ± 8.8 h compared with 18.1 ± 5.4 h in the Amplatzer and 18.8 ± 9.3 h in the Helex group). Specifics regarding procedural complications have previously been described in detail. Briefly, one potential ischaemic event related to the procedure occurred with complete resolution (Helex group). This was most likely related to air embolism or thrombotic material on the device or delivery equipment. Likewise, as previously described, technical difficulties were uncommon with a slightly higher device embolization rate with the Helex device (3 embolizations vs. none with either of the other devices). Periprocedural cardiac tamponade occurred in two patients (one in the Helex and one in the Amplatzer group, respectively). In both cases,
the suspected mechanism was accidental atrial perforation. Percardiocentesis was successful in one and surgery was required in the second patient.\(^4\)

No patients were lost to follow-up. The mean follow-up time was 59.2 ± 6.0 months and did not differ significantly between the three groups (Amplatzer: 59.4 ± 5.0 months; Helex: 59.1 ± 6.5 months; CardioSEAL-STARflex: 59.1 ± 6.5 months).

At 5-year follow-up, the highest complete closure rate was achieved with Amplatzer devices (n = 220; 100%) and the lowest with Helex occluders (n = 213; 96.8%). Complete closure after single device implantation was more common with the Amplatzer and with the CardioSEAL-STARflex than with the Helex occluder (Amplatzer vs. Helex vs. CardioSEAL-STARflex: n = 217 (98.6%) vs. n = 202 (91.8%) vs. n = 213 (96.8%; \(P = 0.0012\)). Likewise, implantation of a second device was most frequently required in patients who received a Helex occluder and least frequently in those treated with an Amplatzer device. Closure rates increased with follow-up duration. While complete defect closure was found in 608 patients 6 months after the intervention (92.1%; n = 211 Amplatzer, n = 189 Helex, n = 208 CardioSEAL-STARflex), at 5 years follow-up, PFO closure was achieved in 652 patients (98.8%; n = 220 Amplatzer, n = 213 Helex, n = 219 CardioSEAL-STARflex).

During follow-up, 24 patients (3.6%) underwent a second intervention for closure of relevant residual shunts. Three of these patients suffered from recurrent cerebral ischaemia prior to the second implantation. In the Amplatzer group, a second device was implanted in two patients. In the first patient, a second Amplatzer occluder was implanted 7 months after the index procedure. In the second patient, a Premere occluder (St Jude Medical, St Paul, MN, USA) was implanted after 25 months. One patient who had been treated with a CardiaStar-occluder prior to randomization and implantation of an Amplatzer occluder underwent explantation of the Amplatzer occluder and operative defect closure due to a severe persistent shunt 12 months after implantation and low likelihood of complete closure with a third device. In the CardioSEAL-STARflex group, seven patients required a second device. In one case, TEE examination at 6 months follow-up showed an atrial septum with multiple fenestrations. These may have been unrecognized at first implantation. A second STARflex device was implanted. The other six residual shunts were closed using Premere in three patients (after 15, 23, and 25 months), Amplatzer in one (after 13 months), and CardioSEAL-STARflex devices in two patients (after 12 and 30 months). In the Helex group, 15 patients underwent a second procedure for residual shunt closure: 1 Premere occluder was implanted after 9 months, 1 Helex device after 16 months, and 11 Amplatzer devices between 1 week and 55 months after the initial procedure. One of these Amplatzer devices was implanted because a TEE at 6 months follow-up revealed a severe shunt due to late device embolization (to the aortic bifurcation). In this case, the transthoracic echocardiography before discharge as well as the TEE 30 days after the intervention showed the device well positioned. Late device embolizations are very rare and there are only few case reports available.\(^{16–18}\) In two patients, implantation of an Amplatzer device was attempted but technically not possible. Of these patients, one underwent surgical defect closure for a large residual shunt 19 months after the implantation.

The combined primary endpoint of TIA, stroke, cerebral death, or paradoxical embolism occurred in 25 patients (3.8%) within 5 years of

<table>
<thead>
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<th>Table 2 Five-year follow-up results</th>
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<tr>
<td><strong>Amplatzer</strong> (n = 220)</td>
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<tr>
<td>Primary endpoint</td>
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<tr>
<td>Peripheral embolism</td>
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<tr>
<td>TIA</td>
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<tr>
<td>Stroke</td>
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<td>Cerebral death</td>
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<td>Thrombus formation</td>
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<td>Atrial fibrillation</td>
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<td>Device embolization</td>
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<tr>
<td>Complete PFO closure</td>
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<tr>
<td>Need of another device implantation for severe residual shunt</td>
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<tr>
<td>Non-neurological death</td>
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<tr>
<td>Vascular death</td>
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<tr>
<td>Complications requiring surgery</td>
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\(^a\)This represents the P-value comparing the Amplatzer device with both, the CardioSEAL-STARflex and Helex device. There was no significant difference between the Amplatzer and Helex device.

\(^b\)This represents the P-value comparing the CardioSEAL-STARflex device with both, the Amplatzer and Helex device. There was no significant difference between the Amplatzer and Helex device.

\(^c\)This represents the P-value comparing the Helex device with both, the Amplatzer and CardioSEAL-STARflex device. There was no significant difference between the Amplatzer and CardioSEAL-STARflex device.
follow-up (Table 2): 10 TIA (1.5%), 12 strokes (1.8%), 3 cases of cerebral death (0.5%), and no paradoxical embolism. In the Amplatzer group, there were significantly fewer events (1.4%; 2 strokes, 1 cerebral death; \( P = 0.042 \)) than in the CardioSEAL-STARflex group (5.9%; 6 TIA, 6 strokes, 1 cerebral death) or in the Helex group (4.1%; 4 TIA, 4 strokes, 1 cerebral death). Survival analysis using the log-rank test demonstrated superiority of the Amplatzer device compared with the CardioSEAL-STARflex (\( P = 0.01 \)) regarding the occurrence of primary endpoint events. Compared with the Helex device, there was a trend to better results with the Amplatzer device (\( P = 0.079 \)). All of the affected patients were examined by neurologists within the context of their endpoint event, and a hospital discharge letter was available for each of these cases.

Regarding the stroke and death rate (3.8% taking all groups into account), there was no significant difference between the three groups (\( P = 0.5827 \)). Likewise, there was no significant difference in the stroke and vascular death rates (2.7% taking all groups into account) between the groups (\( P = 0.1081 \)). The respective hazards are shown in Figure 2.

Two patients in the Amplatzer group suffered from minor strokes at 5 and 19 months after implantation. In both patients, TEE at 1 month follow-up visit excluded residual shunts or thrombus formation on the occluder surface. In addition, one patient died as a consequence of intracranial haemorrhage 4 years after the intervention (no antplatelet or anticoagulation therapy at this time).

In the Helex group, one patient had a TIA (inability to extend the left hand) 30 min after implantation. In this patient, Valsalva manoeuvre immediately after the intervention did not show a residual shunt; hence, the most likely mechanism was air embolism or device- or delivery system-associated thrombus formation undetectable by TEE. In addition, three TIA were reported at 4, 33, and 54 months after the procedures. A mild residual shunt was present in

![Figure 2](https://academic.oup.com/eurheartj/article-abstract/34/43/3362/514364) Cumulative hazards and numbers at risk for (A) the primary endpoint, (B) stroke and death, (C) stroke and vascular death, and (D) any neurological event or necessity of operative intervention.
Percutaneous patent foramen ovale closure with three different devices

one of these patients at follow-up examinations. A stroke occurred in four patients (at 1, 36, 45, and 56 months). In only one of these patients, a residual shunt was present. One patient in the Helex group died from subarachnoid haemorrhage 13 months after device implantation (no antplatelet or anticoagulation therapy at this time).

In the CardioSEAL-STARflex device group, there were six cases of TIA. In one, the TIA occurred within 3 days after the intervention in a patient with large residual shunt after device implantation. Two patients experienced amaurosis fugax 4 and 18 months after the intervention, and three patients reported TIAs between the 4- and 5-year follow-up visits. Neither of these patients had a residual shunt. There were six cases of ischaemic stroke. One minor stroke occurred within 30 days after device implantation. In this patient, TEE at the end of the procedure excluded residual shunting. One patient was hospitalized after echocardiographic detection of right and left atrial thrombus formation on the occluder 2 months after PFO closure. Throughout the hospital stay, a major ischaemic stroke occurred despite anticoagulation. To prevent further embolic events, operative extraction of the intraatrial thrombi was performed. The occluder was removed and the atrial septal defect was closed using a pericardial patch. Four additional strokes have been reported: two within the first year, one after 4 years, and one 5 years after the intervention. A residual shunt could not be detected in any of the affected patients. However, two of the patients had meanwhile developed atrial fibrillation. One patient died due to massive cerebral haemorrhage 3 months after PFO closure (taking dual antiplatelet therapy consisting of aspirin and clopidogrel).

Within 5 years of implantation, 12 patients (11 in the CardioSEAL-STARflex group, 1 in the Helex group) developed a device-associated thrombus. Thrombus formation was significantly more common in the CardioSEAL-STARflex group than in the other groups ($P < 0.0001$). All were seen within 3 months after implantation and 10 resolved after anticoagulation (9 in the CardioSEAL-STARflex group, 1 in the Helex group). Two patients in the CardioSEAL-STARflex group needed operative thrombectomy of large atrial thrombi. Throughout follow-up, no thrombi were observed in the Amplatzer group.

Using these results, we performed an additional endpoint analysis comparing the three groups for a combination of recurrent neurological events and complications requiring surgery. Taking all groups into account, there were 25 neurological events (3.8%; 3 in the Amplatzer group, 9 in the Helex group, 13 in the CardioSEAL-STARflex group) and 6 complications requiring surgery (0.9%; 2 in the Amplatzer group, 1 in the Helex group, 3 in the CardioSEAL-STARflex group) with no significant difference between the three devices ($P = 0.4025$). The respective hazards are shown in Figure 2.

At 5 years follow-up, 40 patients had presented with the new onset of atrial fibrillation (27 in the CardioSEAL-STARflex group, 5 in the Helex group, and 8 in the Amplatzer group). The incidence of atrial fibrillation was significantly higher in the CardioSEAL-STARflex group than in the other groups ($P < 0.0001$). Atrial fibrillation was most often detected within 1 month after device implantation ($n = 18; 4 in the Amplatzer group, 2 in the Helex group, and 12 in the CardioSEAL-STARflex group). In five of these patients, atrial fibrillation began during implantation (one in the Helex group, four in the CardioSEAL-STARflex group). In 25 cases (17 CardioSEAL-STARflex, 3 Helex, and 5 Amplatzer), atrial fibrillation was paroxysmal and sinus rhythm could be maintained with medical therapy.

There were 10 deaths (1.5%) of non-neurological cause at last follow-up. In the Amplatzer group, one patient died in a car accident 2 months and two patients due to cancer 28 and 35 months after implantation. In the Helex group, there were four deaths. Two patients died within 6 months of follow-up, one after 3 months secondary to bilateral pneumonia following an acute myocardial infarction requiring prolonged intensive care, and one of unknown cause. Two patients died of cancer after 30 and 47 months, respectively. In the CardioSEAL-STARflex group, two patients died as a consequence of a myocardial infarction 10 and 25 months after the intervention and one patient due to sudden cardiac death 11 months after the intervention.

Discussion

This study provides long-term data on echocardiographic and clinical findings comparing three different devices for percutaneous PFO closure. Several findings deserve discussion.

First, as previously reported, immediate periprocedural complications and ischaemic events are rare.\textsuperscript{6}

Secondly, complete closure was achieved in the overwhelming majority of patients at last follow-up. Of note, closure rates improved significantly with follow-up time. A residual shunt and need for an additional device was more likely with the Helex device compared with the Amplatzer and CardioSEAL-STARflex devices.

Thirdly, neurological events were uncommon after PFO closure regardless of the device used. Over an observation period of 5 years, a neurological event (stroke, TIA, or cerebral death) occurred in 25 of 660 cases (3.8%). This translates into an annual recurrent event rate of 0.77% for the entire population (Amplatzer: 0.28%; CardioSEAL-STARflex: 0.83%; Helex: 0.77%), and therefore compares favourably with the reported annual 3–4% recurrence rate of TIA or stroke in the absence of PFO closure.\textsuperscript{19,20} and previously published long-term results after defect closure.\textsuperscript{8} Windecker et al.\textsuperscript{6} reported a recurrent ischaemic event rate after PFO closure (with six different devices, the majority of which were Amplatzer PFO or ASD occluders) of 8.5% at 4-year follow-up. They demonstrated a trend towards a lower rate of neurological events compared with a non-randomized control group treated medically (24.3%; $P = 0.05$; 95% CI 0.23–1.01). In CLOSURE I, comparing device closure and medical therapy in patients with PFO and cryptogenic stroke, the stroke rate after percutaneous closure at 2 years follow-up was 2.9%.\textsuperscript{8} The CardioSEAL-STARflex device was used exclusively in this trial. In comparison with the results of CLOSURE I, the stroke rate using this specific device in our analysis at 2 years follow-up was 2.3%.

Fourthly, in the majority of patients with events, there was no residual shunt (1 CardioSEAL-STARflex case, 2 Helex cases; $P = 0.4653$), atrial fibrillation (2 CardioSEAL-STARflex cases; $P = 0.366$), or device associated thrombus (1 CardioSEAL-STARflex case; $P = 0.6188$). This supports observations reported by Wallenborn et al.\textsuperscript{21} that, in the majority of patients with recurrent events after PFO closure, there is no residual shunt and raises the possibility that, in these cases, the PFO may have been an innocent bystander for the initial event. Indeed, in some patients, risk factors for
stroke beyond the PFO may be present. Hence, eliminating the PFO only has an impact on one of many risk factors. Moreover, a device-associated thrombus or intermittent atrial fibrillation both of which may be related to the PFO or device but not captured at follow-up are conceivable.

Fifthly, and most importantly, in our study, the events the devices were intended to prevent (strokes and TIA’s) were significantly less common after Amplatzer implantation compared with both other devices. Importantly, after adjusting for other variables, there remained a strong trend towards a higher rate of the primary endpoint with the CardioSEAL-STARflex device. Thrombus formation and atrial fibrillation were more common after CardioSEAL-STARflex implantation (5 and 12%, respectively) compared with the other devices and both, thrombus formation and atrial fibrillation were independent predictors of neurological complications and complications requiring surgery. Similarly, Schwerzman et al. reported differences in event rates comparing two devices in a non-randomized fashion, the Amplatz PFO occluder and PFO STAR device. There was a trend towards less recurrent events with the Amplatzer PFO occluder compared with the PFO STAR device.25 These findings have major implications for trials comparing percutaneous PFO closure with other treatment modalities in patients with cryptogenic strokes. Event rates may differ depending on the type of device used. Moreover, it suggests that caution should be exercised interpreting the results of CLOSURE I. It is conceivable that a higher incidence of device-related thrombus formation (1.1%) and atrial fibrillation (6%) with the CardioSEAL-STARflex device counterbalanced the potential benefit anticipated with PFO closure. In contrast, the incidence of atrial fibrillation and device-related thrombus formation was very low after Amplatz occluder implantation in our study (3.6 and 0%, respectively) and in both, the RESPECT (0.4% respectively) and PC trials (2.9 and 0%, respectively). In this context, in an as-treated analysis of the recently presented results of the RESPECT trial, comparing the Amplatz PFO occluder with medical therapy in patients with cryptogenic stroke, at 2 years, ischaemic events were less common in the device group. Similarly, the stroke rate in the PC trial, when the stroke definition of the RESPECT trial was applied, was lower after device closure using the Ampltzer PFO occluder.10 The neutral findings of CLOSURE I on the one hand, and results of RESPECT and PC slightly favouring PFO closure on the other, support that type of implanted device may impact the efficacy of PFO closure when compared with medical therapy.

Sixthly, feared and potentially lethal late device erosion is a very rare event. In the AGA Registry, the incidence of this complication was very low (0.018%).23 However, due to voluntary notification, the true incidence may have been underreported. Delaney et al.24 reported a slightly higher incidence at 0.3%. Erosion does not appear to be unique to one device as it has been reported with others including the STARflex device.25

Finally, patients who have undergone successful PFO closures need follow-up examinations, particularly in the early period after implantation as device-associated thrombus formation, late embolization, and atrial fibrillation can occur all of which may lead to cerebral events thereby offsetting the desired benefit of PFO closure.

Of note, device selection in our centre has changed because the CardioSEAL-STARflex is no longer commercially available. The Helex device has, in the meantime, undergone a number of technical changes.

**Limitations**

This was a single centre, single operator study. The results and conclusions may not be transferable or applicable to other settings. Information on antithrombotic therapy was not available at long-term follow-up. Hence, it cannot be excluded that differences in the anticoagulant regimen between device groups contributed to differences in outcome.

The course of migraine was not a predetermined endpoint and follow-up data on this parameter were not sufficiently achieved in order to be included in our analysis.

At the time of study initiation, data regarding the long-term event rates and differences between devices as well as differences compared with medical therapy were not available. Therefore, we were unable to perform a meaningful sample size calculation and power analysis for the long-term endpoint. Therefore, this randomized trial may be underpowered regarding long-term event rate comparisons among closure devices.

Further, as this is a comparison between three different PFO occluders and not a comparison between PFO closure and medical therapy, definitive statements regarding the general long-term efficacy of PFO closure in the prevention of embolic events cannot be made. Likewise, our study cannot be fully conclusive as other currently available devices had not been studied. Several follow-up modalities were allowed and routine long-term follow-up using cerebral imaging (CT or MRI) was not performed. Therefore, the incidence of silent cerebral events may have been underestimated. Furthermore, the investigators were not blinded to the device; therefore, observer bias cannot be ruled out.

**Conclusion**

Percutaneous PFO closure is safe. The overall incidence of neurological events after closure is low. However, there appear to be significant differences in the neurological event rate between devices. Hence, the choice of device may determine the efficacy of PFO closure. This has important implications for future PFO trial designs and interpretation.

**Conflict of interest:** Prof. H. S. has received study honoraries, travel expenses or consulting fees from AGA Medical, W.L. Gore and NMT Medical, the manufacturers of the device subjects of this manuscript.

All other authors have no conflicts of interest.

**References**

Percutaneous patent foramen ovale closure with three different devices